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Treatment Options for Thrombocytopenia in Patients With Chronic Liver Disease Undergoing a Scheduled Procedure

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Abstract: Thrombocytopenia is a consequence of portal hypertension and is the most common hematological manifestation of chronic liver disease (CLD) (ie, cirrhosis). Data indicates the rates of CLD are increasing and, as a result, so will the incidence of this complication. Although bleeding risks are only relevant when elective procedures are performed, this is a frequent concern as these procedures are commonly part of the spectrum of care for patients with cirrhosis. As such, thrombocytopenia remains a pertinent issue. Fortunately, we now have effective and accurate treatment modalities to raise platelet counts before scheduled procedures, known as thrombopoietin receptor agonists. Two drugs in this therapeutic class (avatrombopag and lusutrombopag) are now approved for the treatment of thrombocytopenia in adults with CLD undergoing a procedure and have revolutionized how this is managed. Although there is progress in the field, peer-reviewed literature and expert guidance are lacking. Recognizing these unmet needs, a group of expert hepatologists comprised this review, which summarizes the most current and relevant peer-reviewed literature on thrombocytopenia in CLD and provides clinical expertise on this timely topic.

Key Words: thrombocytopenia, chronic liver disease, treatment, procedure

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Although thrombocytopenia, that is, reduction of platelet count in the blood, is the single most common hematological manifestation of chronic liver disease (CLD), published literature on this topic is scarce. As the incidence of thrombocytopenia in CLD is 70% in patients with cirrhosis versus 6% in patients without cirrhosis, for the purposes of our understanding of thrombocytopenia, CLD essentially refers to cirrhosis throughout this review. In the United States, nearly 4 million adults (1.6% of the population) have CLD.[1] In fact, CLD and cirrhosis were the 12th leading cause of death in the United States in 2015, taking the lives of over 40,000 patients in that year.[2] An epidemiology study published that same year reported a 2-year mortality rate of 26.4% for patients with cirrhosis.[3]

According to the American Association for the Study of Liver Diseases (AASLD), cirrhosis is a heterogeneous disease that cannot be studied or managed as a single entity.[4] As such, this advanced form of liver disease is most commonly the result of nonalcoholic fatty liver disease, chronic hepatitis C virus (HCV), and alcoholic liver disease. These diseases pose a significant burden to patients and providers and are continuing to increase in prevalence (Table 1). In fact, a recent population-based study from Kim and colleagues provided an updated estimate of the burden and etiology-specific mortality of CLDs in the United States. They found that between 2007 and 2013, there was a decrease in HCV-related mortality, which coincided with the introduction of the highly effective direct-acting antiviral therapies. Conversely, mortality from alcoholic liver disease and nonalcoholic fatty liver disease increased during the same period.[12] Furthermore, as described in the table, the effects of CLD are becoming more noticeable in a younger cohort of patients,[8,13] even with regard to HCV. Other less common causes of cirrhosis include chronic hepatitis B, autoimmune hepatitis, exposure to toxic chemicals and/or drugs, bile duct disorders, and inherited conditions.[14]

As the burden of CLDs increase, so will the prevalence of cirrhosis and cirrhotic complications. Portal hypertension is the initial and main consequence of cirrhosis and is responsible for the majority of its complications,[4] including thrombocytopenia. Thrombocytopenia is classified according to platelet count as mild (> 75,000 to <150,000/μL), moderate (50,000 to 75,000/μL), or severe (< 50,000/μL; Fig. 1).[15] The presence of severe thrombocytopenia can significantly complicate the routine care of cirrhotic patients; standard procedures (eg, liver biopsies, medically-indicated surgeries) can pose a substantial risk of bleeding.[16–18] As such, most guidelines established by major medical societies recommend treatment interventions for patients with platelet counts <50,000/μL to reduce bleeding risk.[19–21] In 2018, 2 new drugs, avatrombopag and lusutrombopag, were approved by the Food and Drug Administration (FDA) for thrombocytopenia in adults with CLD

TABLE 1. The Increasing Burden of CLD

Type of CLD	Epidemiology Data	Epidemiologic Projections
NAFLD	Approximately 26% of adults in the United States have NAFLD; 3%-5% have nonalcoholic steatohepatitis* (NASH; defined as > 5% hepatic steatosis and inflammation with hepatocyte injury)†	The burden of NASH is expected to increase from 16.5 million in 2015 to 27 million in 2030 because of increased rates of contributing factors (obesity and diabetes mellitus)[5]
HCV	According to the CDC, ~3.5 million people in the United States have HCV.‡ Increasing cure rates may have resulted in a decrease in prevalence In 2015, ~20,000 deaths were attributed to HCV[6] Most commonly seen in patients born from 1945 to 1965 (ie, baby boomers),§ who are at a much greater risk of HCV-related mortality[6]	Cases reported to the CDC tripled from 2010 to 2015[6] The highest overall number of new infections is now among 20- to 29-year-old because of increasing injection opioid use and increased transmission[6] Unlike baby boomers, young patients have no concentrated HCV-screening efforts and are not engaged in the health care system
ALD	In 2015, of the 78,529 liver disease deaths among individuals aged 12 and older, 47% involved alcohol‖ Approximately 15.1 million adults had AUD in 2015[7]	The National Epidemiologic Survey on Alcohol and Related Conditions was administered to ~80,000 patients, revealing that, between 2001-2002 and 2012-2013, 12-month alcohol use, high-risk drinking, and DSM-IV AUD *increased* by 11.2%, 29.9%, and 49.4%, respectively. Investigators deemed this a "public health crisis"¶

Among all deaths from cirrhosis in 2013, 47.9% were alcohol-related; this was highest in patients aged 25-34 (76.5%), followed by patients aged 35-44 (70%).[8]
*Estes et al.[5]
†Chalasani et al.[9]
‡Hepatitis C FAQs for Health Professionals.[6]
§Hepatitis C.[10]
‖Alcohol Facts and Statistics.[7]
¶Grant et al.[11]
ALD indicates alcoholic liver disease; AUD, alcohol use disorder, defined by the National Institute on Alcohol Abuse and Alcoholism as a chronic relapsing brain disease characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using; CDC, centers for disease control; DSM, diagnostic and statistical manual of mental disorders; FAQ, frequently asked questions; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic hepatic steatosis.

undergoing a procedure.[22,23] These new agents have revolutionized the treatment of thrombocytopenia in CLD.

Given the new developments and the shortage of peer-reviewed literature on thrombocytopenia, the Chronic Liver Disease Foundation (CLDF) identified the need and obtained grant-funding to produce a publication on this topic. A small group of expert hepatologists, who are also CLDF members, were selected and convened in the form of a workshop, during which the most current and relevant peer-reviewed literature on thrombocytopenia was evaluated and conferred. The meeting presentations and detailed discussions that followed are summarized in this article. The intent of this publication is to provide practicing clinicians with a timely and useful review of the current knowledge of thrombocytopenia, expert direction on the management of thrombocytopenia in patients with liver disease undergoing a scheduled procedure, and treatment updates in the field of thrombocytopenia.

PATHOGENESIS

To understand the mechanisms by which thrombocytopenia develops in CLD, an initial discussion is warranted on the mechanisms of normal, healthy platelet production.

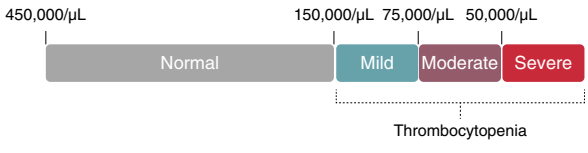

FIGURE 1. Thrombocytopenia classified according to platelet count.[15] Threshold values defined by Afdhal et al.[15] full color online

Thrombopoietin (TPO) is a glycoprotein hormone produced primarily by the liver but also the kidneys. Although the role of TPO is not completely understood, it appears that TPO is an important regulator of platelet production. TPO, also known as megakaryocyte growth development factor (MGDF), has an affinity for platelet precursor cells in the bone marrow called megakaryocytes.[24] TPO binds to the megakaryocyte c-Mpl receptor, inducing phosphorylation of this receptor and stimulating several other molecules in numerous signal transduction pathways.[25–27] The resultant multi-step process is known as thrombopoiesis; this involves prevention of megakaryocyte apoptosis, improvement of cell viability, promotion of growth, and increased differentiation of megakaryocytes into platelets (Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JCG/A552).[28]

TPO serves as a regulator of platelet production. During thrombopoiesis, the threshold for platelet activation by other known agonists (eg, adenosine diphosphate and collagen) is significant.[25–27] By mechanisms not completely understood, TPO levels are inversely proportional to total platelet mass.[29,30] Although TPO appears to dominate platelet regulation, it has no other regulatory role in the production of other blood products, such as leukocytes and erythrocytes.[31]

In healthy individuals, 35,000 to 50,000 platelets are produced daily and production is proportional to demand. Once produced, platelets survive in circulation for 8 to 10 days. Senescent platelets are removed by monocytes and macrophages of the reticuloendothelial system.[32] The liver plays a small role in this removal; liver receptors, known as Ashwell Morell receptors, recognize alterations in the glycan pattern on the surface of platelets and remove de-sialylated platelets.[33] The

spleen, however, is responsible for the majority of platelet elimination. In fact, one third of the total platelet mass is found in the spleen at any given time. The spleen removes old platelets as blood moves through it; this blow-flood dependent process is analogous to a waterwheel effect.[32]

There are 4 principal mechanisms by which a patient can develop thrombocytopenia. These include (1) decreased platelet production; (2) increased destruction/consumption of platelets; (3) dilution of platelets and; (4) increased platelet sequestration. There is no research that indicates what percentage of thrombocytopenia is divided among these 4 mechanisms, but it is known that CLD can contribute to each mechanism (Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JCG/A552).[15,17,32] For example, although disorders of TPO and the c-Mpl receptor can be a result of various causes (eg, familial gene mutations, administration of the anti-TPO antibody PEG-rHuMGDF, amegakaryocytic thrombocytopenia, and absent TPO receptor, myeloproliferative disorders), they are quite often the result of cirrhosis.[32] When comparing cirrhotic patients to healthy controls, decreased hepatic production of TPO is observed in the former group. After liver transplantation, however, TPO levels return to normal.[34] In addition, cirrhosis is often associated with portal hypertension and secondary splenomegaly. In this case, the total body platelet count is normal, but 90% of platelets are redistributed into the spleen, resulting in thrombocytopenia as a result of increased sequestration.[32]

CLINICAL SIGNIFICANCE OF THROMBOCYTOPENIA: PORTAL HYPERTENSION AND LIVER DISEASE SEVERITY

Portal hypertension is often the initial and main consequence of cirrhosis and is responsible for a majority of its complications, notably thrombocytopenia. This clinical syndrome essentially results from an abnormal elevation of portal venous pressure caused by increased hepatic resistance to portal flow and increased portal venous in-flow. A more comprehensive explanation of portal hypertension is demonstrated in Supplementary Figure 2 (Supplemental Digital Content 2, http://links.lww.com/JCG/A553).

The hepatic venous pressure gradient (HVPG), measured via balloon catheterization of a hepatic vein, is the gold standard for determining portal pressure. An HVPG elevation >5 mm Hg is considered portal hypertension; the degree of HVPG elevation determines the sub-staging of the condition and has important prognostic implications (Table 2).[4,41] Although the greater the degree of portal hypertension is associated with a greater risk of related complications, the opposite is even truer; the lack of portal hypertension has good negative predictive value especially for the risk of developing ascites and variceal bleeding. In other words, the association between portal hypertension and related complications is not perfectly linear.

It is important to emphasize that portal hypertension can be diagnosed without a formal, anatomic diagnosis of cirrhosis. In fact, the term "compensated advanced CLD" has been proposed to better describe noncirrhotic patients with portal hypertension. Regardless, the diagnosis of portal hypertension with or without cirrhosis warrants close monitoring and treatment by a liver specialist.[4,42]

There are many consequences of portal hypertension (Supplementary Table 1, Supplemental Digital Content 3, http://links.lww.com/JCG/A554) and each consequence rightfully warrants its own publication. With regard to this review, the focus will be on splenomegaly and hypersplenism because, in the setting of CLD, this is the primary cause of thrombocytopenia. Specifically, portal hypertension increases splenic arterial blood flow and diminishes splenic venous flow into the portal vein. Congestive splenomegaly occurs, that is, congestion of intrasplenic blood flow and spleen enlargement, resulting in thrombocytopenia,[43] anemia, and/or leukopenia (either alone or in combination).[44,45] In fact, severe cytopenias are detected in up to one third of all patients being assessed for liver transplantation.[46]

Platelet counts are readily available and extremely useful to practitioners. A low platelet count is the most common laboratory sign of portal hypertension, but there are no reliable platelet cutoff points that predict the natural history or outcome of CLD. In general, the lower the platelets, the poorer the prognosis. For example, platelet counts <20,000/μL are correlated with poor outcome in patients with acute-on-chronic liver failure.[47] Overall, platelets should be assessed in all CLD patients since thrombocytopenia indicates portal hypertension and severe forms increase bleeding risk during procedures.

TABLE 2. Stages of Portal Hypertension

Portal Pressure (HPVG)	Stage	Prognostic Implications
6-9 mm Hg	Mild	Portal hypertension will worsen as the degree of liver fibrosis increases
≥ 10 mm Hg	Clinically significant portal hypertension	Increased risk of developing varices,* overt clinical decompensation,† postsurgical decompensation,‡ and hepatocellular carcinoma§ The presence of varices is associated with poorer prognosis‖¶

*Groszmann et al.[35]
†Ripoll et al.[36]
‡Bruix et al.[37]
§Ripoll et al.[38]
‖Bruno et al.[39]
¶Zipprich et al.[40]
HPVG indicates hepatic venous pressure gradient.

CLINICAL SIGNIFICANCE OF THROMBOCYTOPENIA: PORTAL PROCEDURES IN PATIENTS WITH CLD

Patients with cirrhosis are classified as compensated or decompensated depending on laboratory values (eg, low albumin levels) or the presence or absence of clinically evident, overt events (eg, ascites, variceal hemorrhage, hepatic encephalopathy); the presence of decompensating events markedly shortens survival.[4] The severity of cirrhosis can help direct measures to anticipate and prevent complications as, in general, the greater the severity of cirrhosis, the more difficult it may be to correct the complication(s). The model for end-stage liver disease (MELD) score is a continuous measure of liver disease severity that serves as an accurate predictor of 3-month mortality. The addition of sodium level to the MELD score (MELD-Na) improves the performance of the model to predict mortality. The MELD-Na calculation is based on the objective parameters, sodium,

creatinine, bilirubin, and the international normalized ratio (INR), and is, therefore, independent of disease etiology and complications of portal hypertension. MELD scores can range from 6 (less ill) to >40 (gravely ill).[48,49] Another classification, known as the Child-Turcotte classification (or Child-Pugh score), is based on 3 clinical, subjective parameters (ascites, encephalopathy, and nutritional status) and 2 biochemical, objective parameters (serum albumin and bilirubin). Each parameter is given a point-based score and a combined score is used to classify the patient as Child-Pugh A, B or C, corresponding to none or minimally, moderately, or severely altered hepatic functional reserve, respectively.[50]

Thrombocytopenia can occur in both the compensated and decompensated stages, but without interventional procedures, there is little or no risk of spontaneous bleeding because of the low platelet count, although the presence of thrombocytopenia can predict the presence of varices that may be at risk of rupturing. In addition, patients with cirrhosis often require procedures for routine care and to manage complications (Table 3); this is when the presence of thrombocytopenia should be assessed by treating clinicians.

As previously noted, one example of a cirrhotic complication that is of concern in a thrombocytopenic patient is the detection of large varices. Varices are portosystemic collaterals (formed as a result of portal hypertension, Supplementary Fig. 2, Supplemental Digital Content 2, http://links.lww.com/JCG/A553) that can rupture and cause variceal hemorrhage, the most common lethal complication of cirrhosis. The gold standard in the diagnosis of varices is esophagogastroduodenoscopy (EGD).[51] Patients with normal platelet counts (>150,000/μL) and low liver stiffness (<20 kPa on Fibroscan) have a very low probability (<5%) of having high-risk varices; EGD can be circumvented in this case.[42] In patients who do not meet these criteria, however, EGD is recommended on the diagnosis of cirrhosis and if varices are detected, variceal ligation (ie, banding) may be required.

Although bleeding risks are apparent and precautions are necessary, guidance is lacking in the peer-reviewed literature. A recent societal guideline noted that definitions of coagulopathy and thrombocytopenia and threshold laboratory values (INR, platelets) that are not considered acceptable for endoscopy and surgery have not been clearly established.[52] In fact, prothrombin time and INR do not predict bleeding episodes in those with liver disease; in the case of liver disease, only the procoagulant pathway, not the anticoagulant pathway, is assessed. Similarly, platelet counts are not routinely assessed before endoscopy in the general population, although platelet counts are routinely ordered in those with cirrhosis.

Because of the lack of clearly established guidelines, there is no consensus in the literature on the cutoff for platelet count and INR for variceal ligation without gastrointestinal bleeding. As a result, these cutoffs vary among institutions. Many societies do, however, have accepted guidelines for appropriate platelet levels when considering interventional procedures with bleeding risk (Table 4).

In conclusion, the following recommendations can be made with regard to INR and platelets. INR, a measure of the extrinsic pathway of coagulation, is often found to be elevated in CLD. However, an elevated INR does not inherently reflect a coagulation defect; there are no assays readily available to measure the fibrinolytic pathway. Cirrhotic patients can be at risk for thrombotic, as well as postprocedure bleeding episodes, the latter of which can be evaluated via platelet counts. As previously recommended, platelet counts should be obtained in cirrhotic patients, especially when considering an elective procedure.

TREATMENT OPTIONS FOR THROMBOCYTOPENIA

There are opportunities to prevent and manage periprocedural bleeding in patients with thrombocytopenia and CLD. Treatment was previously limited to platelet transfusions, transjugular intrahepatic portosystemic stent placement, and splenic artery embolization,[55–58] which are not without limitations, as detailed in Table 5.

In recent years, TPO receptor agonists, which have been used routinely for the treatment of thrombocytopenia associated with other conditions, are being used in CLD (Table 5).[55] Drugs in this therapeutic class, which include eltrombopag, romiplostim, avatrombopag, and lusutrombopag, increase platelet production through interactions with the TPO receptor on megakaryocytes, specifically c-MpL

TABLE 3. Common Elective Procedures in Chronic Liver Disease That are Associated With Risk of Bleeds

Gastroenterological procedures	Colonoscopy with polypectomy
	Endoscopic retrograde cholangiopancreatography
	Endoscopy with ligation paracentesis
	Thoracentesis
	Liver biopsy
Nongastroenterological procedures	Cardiac catheterization
	Dental procedures
	Interventional radiologic procedures (eg, transjugular intrahepatic portosystemic shunt, ablation of hepatocellular carcinoma)

TABLE 4. Guideline Recommendations for Appropriate Platelet Levels for Transfusions Based on Procedures

Guideline	Year	Recommendation
American Association for the Study of Liver Diseases[19]	2009	Platelet transfusion should be considered when levels are <50-60,000/μL
American Society for Gastrointestinal Endoscopy[20]	2012	Platelet threshold 20,000/μL for diagnostic endoscopy; 50,000/μL if biopsy performed
American Society of Hematology[18]	2013	Platelet threshold for any invasive procedure 50,000/μL
American Society of Clinical Oncology*	2001	Platelet count 40-50,000/μL is sufficient for major invasive procedures in the absence of coagulation abnormalities
American Association of Blood Bankers†	2015	Platelet threshold for any invasive procedure 50,000/μL

*Szczepiorkowski et al.[53]
†Weiss et al.[54]

TABLE 5. Traditional Treatments for Thrombocytopenia

Treatments	Considerations	Hepatology Panel Recommendation
Platelet transfusions	Multiple units required to achieve the target platelet count Risk of transfusion reactions (fever, nonhemolytic, and allergic reactions) Increases portal hypertension Prolonged hospitalization Risk of infection and sepsis Short half-life Platelet refractoriness due to HLA alloimmunization (occurs in up to 40% of patients)	Yes
TPO agonists	Use before invasive, CLD-related procedures is relatively recent Two agents are approved in CLD; individual patient factors dictate agent selection Strategic scheduling required; administration necessary for a specific number of days before the procedure	Yes
Transjugular intrahepatic portosystemic stent placement	Few studies on use for thrombocytopenia; more are needed Unknown which factors may predict who will respond Potential adverse events include liver failure and hepatic encephalopathy TPO levels are not expected to increase	No
Splenic artery embolization	Temporary improvement in leukocyte and platelet counts Numerous morbidities (mortality rates 0%-6%) Associated with postembolization syndrome (pain, fever, nausea, vomiting) Complication rates 15%-30%; include pleural effusion and/or ascites, portal vein thrombosis, splenic abscess	No

CLD indicates chronic liver disease; HLA, human leukocyte antigen; TPO, thrombopoietin.

ligand-mediated activation of the JAK-STAT and MAP kinase pathways.[59–61] Use of these TPO agonists for treating thrombocytopenia before invasive procedures in CLD patients is relatively recent but has proven to be accurate and effective. Here, we present the therapeutic options and relevant data, with a focus on the 2 approved therapies for CLD. The information offered here can help guide the selection of a TPO agonist, taking each individual patient into consideration as well.

The first-generation TPO agonists, eltrombopag and romiplostim, are both FDA-approved for thrombocytopenia due to other conditions but do not specifically carry indications for use in patients with CLD.[62,63] Romiplostim is administered via weekly subcutaneous injections and is not actively being developed for thrombocytopenia in CLD; anecdotal case report data and studies in small populations of CLD patients are available.[64–66] Eltrombopag, an oral agent, has been more broadly studied for use in CLD.

The most recently published eltrombopag data in CLD is from the ELEVATE study (Eltrombopag Evaluated for Its Ability to Overcome Thrombocytopenia and Enable Procedures), a phase 3, international, double-blind, placebo-controlled trial. ELEVATE assessed the utility of eltrombopag to increase platelet counts and reduce the need for platelet transfusions in patients with thrombocytopenia and CLD who were undergoing an elective invasive procedure. Of the 292 adult subjects that were enrolled, 252 (86%) had clinically proven or biopsy-proven cirrhosis (10% had Child-Pugh C with a score of 10 to 12 and MELD, score ≤ 24) with a platelet count of <50,000/μL. Patients were randomly assigned to receive eltrombopag, at a dose of 75 mg daily, or the placebo for 14 days before a planned elective invasive procedure that was performed within 5 days after the last dose. The primary endpoint of ELEVATE, which was the avoidance of a platelet transfusion before, during, and up to 7 days after the procedure, was achieved in significantly more patients who received eltrombopag compared with the placebo (72% vs. 19%, respectively; $P < 0.001$). No significant difference between the eltrombopag and placebo groups was observed in bleeding episodes of World Health Organization (WHO) grade 2 or higher (17% and 23% of patients, respectively). The incidence and severity of adverse events (AEs) were similar in the eltrombopag and placebo groups with the exception of thrombotic events, which were observed in more patients in the eltrombopag group versus the placebo (6 vs. 1, respectively).[67]

In 2018, 2 oral, selective TPO agonists, avatrombopag and lusutrombopag, were approved by the FDA for thrombocytopenia in adults with CLD undergoing a procedure.[22,23,28,29] The safety and efficacy of avatrombopag in increasing platelet counts in CLD were evaluated in 2 pivotal phase 3 studies, ADAPT-1 and ADAPT-2. These randomized, placebo-controlled studies, which took place in ~150 study sites in 36 countries, included adults with thrombocytopenia and CLD undergoing scheduled procedures (n = 231 and 204, respectively). Patients were placed into a low baseline platelet count cohort (< 40,000/μL) or a high baseline platelet count cohort (40,000 to <50,000/μL) and within each cohort were randomized (2:1) to receive avatrombopag 60 mg/d (low platelet cohort) or 40 mg/d (high cohort) or placebo for 5 days. The primary endpoint was the proportion of patients

TABLE 6. Drug Administration and Scheduling of Procedures When Initiating Second-Generation Thrombopoietin Agonists in Chronic Liver Disease Patients

Approved Drug	No. Days Dosed *Before* the Procedure	No. Days Dosed	No. Days *After the Last Dose* That Procedure Needs to be Performed Within	No. Days Platelets Return Back to Baseline (After Initial Dosing Date)
Avatrombopag[22]	10-13	5	5-8	30-36*
Lusutrombopag[23]	8-14	7	2-8	35-36

*Reported data did not capture timepoints of platelet levels from days 18 to 36.

not requiring platelet transfusions or rescue procedures for bleeding up to 7 days after a scheduled procedure.[68]

Significantly more patients in ADAPT-1 and ADAPT-2 met this endpoint compared with the placebo. Specifically, in ADAPT-1, 65.6% and 88.1% of patients (60 mg and 40 groups, respectively) met this endpoint compared with 22.9% and 38.2% of patients receiving the placebo ($P < 0.0001$ for both). In ADAPT-2, 68.6% and 87.9% of patients (60 and 40 mg groups, respectively) met this endpoint compared with 34.9% and 33.3% of patients who received the placebo ($P < 0.001$ for both). In both studies, the time course for the increase in platelet counts after avatrombopag administration was similar; administration of avatrombopag resulted in platelet increases by day 4, peak at days 10 to 13, and return to baseline levels by day 35.[68]

Overall, the safety profile of avatrombopag in both studies was similar to the placebo, with a comparable overall incidence of treatment-emergent AEs in avatrombopag- and placebo-treated patients in both the low and high baseline platelet count cohorts. The most reported AEs across both studies were mild-to-moderate in severity in all treatment groups and included abdominal pain, dyspepsia, nausea, pyrexia, dizziness, and headache. The overall incidence of serious AEs in both studies was low and similar in both the combined avatrombopag- and placebo-treatment groups; investigators categorized these AEs as "consistent and to be expected in a CLD patient population."[68]

The approval of lusutrombopag was based on the results of L-PLUS 1, a Japanese, phase 3, double-blind, parallel-group study of 96 patients with CLD and thrombocytopenia (platelet counts <50,000/μL) undergoing invasive procedures. L-PLUS 1 met the primary endpoint; the proportion of patients who did not require preoperative platelet transfusions was significantly greater in the lusutrombopag group versus the placebo group (79.2% vs. 12.5%, respectively; $P < 0.0001$). Among patients not receiving platelet transfusions, the median platelet count reached ≥ 50,000/μL after 5 days, and the maximum platelet count was reached after a mean of 13.4 days. Furthermore, no significant safety concerns were raised in this study. Adverse drug reactions were reported in 8.3% of patients in the lusutrombopag group and 2.1% of patients in the placebo group.[69]

The safety and efficacy of lusutrombopag in this patient population was confirmed in a larger, global, phase 3, double-blind, placebo-controlled study (L-PLUS 2). This recently published study randomized 215 patients, with CLD and baseline platelet counts <50,000/μL, to once-daily lusutrombopag 3 mg or placebo ≤7 days before an invasive procedure scheduled 2 to 7 days after the last dose. The intent-to-treat population included all randomized patients and was the primary population for the efficacy analysis. The per-protocol population included all randomized patients who had no major protocol deviations pertaining to the efficacy evaluation. The primary endpoint was avoidance of preprocedure platelet transfusion and avoidance of rescue

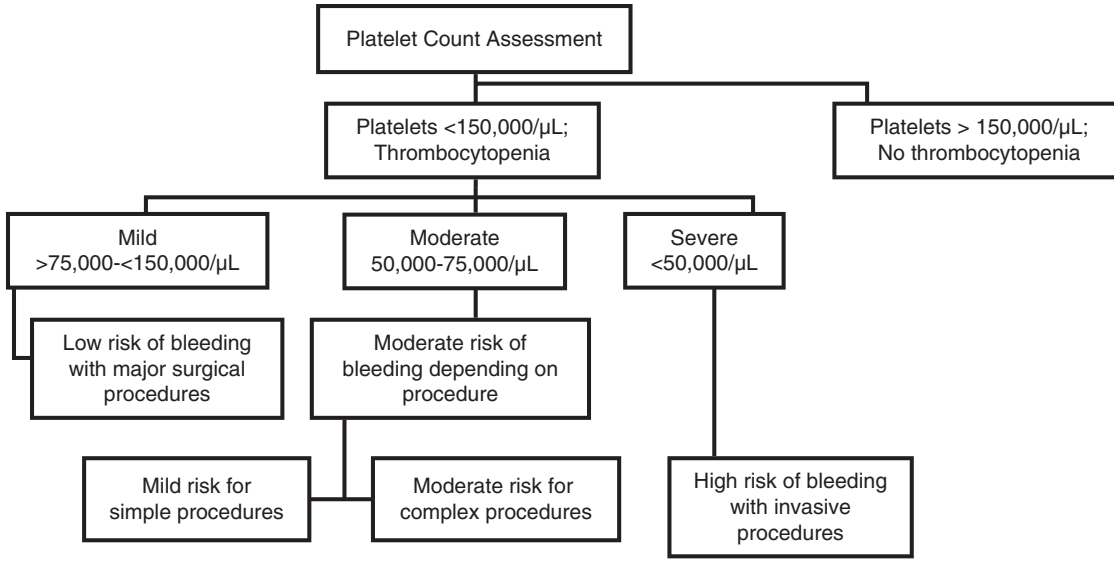

FIGURE 2. Clinical algorithm for assessing platelet counts, diagnosing thrombocytopenia and determining bleeding risk in chronic liver disease in patients undergoing procedures.

therapy for bleeding; in the intent-to-treat population, significantly more patients in the lusutrombopag group (64.8%, 70/108) met this endpoint compared with the placebo group (29.0%, 31/107; $P < 0.0001$). In a sensitivity analysis using the per-protocol population, 72.5% (66/91; 95% confidence interval: 62.2, 81.4) and 20.2% (18/89; 95% confidence interval: 12.4, 30.1) of patients met the primary endpoint ($P < 0.0001$). The median duration of time that platelet counts remained $\geq 50{,}000/\mu L$ for patients who received lusutrombopag and no platelet transfusions (n = 74) was 19.2 days versus 0.0 days for patients who received placebo and platelet transfusions (n = 73; $P < 0.0001$). In addition, the median maximum change in platelets from the baseline was over 4 times higher for patients treated with lusutrombopag who did not receive platelet transfusions than for patients treated with the placebo who did receive platelet transfusions (45,000 vs. 11,000/μL).[70]

Overall, 47.7% (51/107) of patients in the lusutrombopag group and 48.6% (52/107) in the placebo group had at least one treatment-emergent AE. Most AEs were considered mild or moderate in severity with the most common being headache, abdominal pain, fatigue, peripheral edema, and nausea. There were 3 mild bleeding events in 3 patients in the lusutrombopag group (2.8%) and all were considered mild. There were 7 bleeding events in 6 patients in the placebo group (5.6%); 2 bleeding events were considered as mild, 4 moderate, and 1 severe.[70]

As the data presented demonstrate, both avatrombopag and lusutrombopag can safely and effectively increase platelets in thrombocytopenic CLD patients undergoing a scheduled procedure. In addition, drug interactions do not appear to be an issue. The risks of bleeding differ depending on the procedure performed, and these risks can be stratified into high or low. However, the use of TPO agonists is stratified by the FDA according to absolute platelet count, not bleeding risk by procedure. In summary, TPO agonists are indicated to be used for invasive procedures whenever a platelet value is $<50{,}000/\mu L$, regardless of bleeding risk.

Strategic scheduling is required when using either of these drugs, as both labels indicate that administration is necessary for a certain number of days before the procedure and the procedure must be performed within a certain number of days after the last dose (Table 6). Because of the several-day lag for platelet production, TPO agonists should not be used for emergent cases. It is also important to remember that, when thrombocytopenia and bleeding are a concern, improving platelet counts is not only important on the day of the procedure, but also 10 to 12 days postprocedure to avoid secondary bleeding. The number of days involved in clot formation may not matter, the big concern is after the event. The majority of the time, late bleeding occurs no > 10 to 12 days postprocedure.[70]

CONCLUSIONS

Peer-reviewed literature and expert guidance have been lacking with regard to the evaluation and management of thrombocytopenia in patients with CLD, but useful tools are available and accessible. Platelet counts are readily available in clinical practice and approved therapies have demonstrated effective and safe increases in platelets before necessary procedures, allowing for them to be performed without platelet transfusions. As such, this is an opportune time to publish this comprehensive and expert hepatologist-led review of thrombocytopenia in liver diseases, which will surely allow clinicians to better serve these patients. In conclusion, we offer an algorithm to reference when assessing platelet counts, diagnosing thrombocytopenia, and determining bleeding risk in CLD patients (Fig. 2).

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